

REMARKS

Previously, claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 were pending and under consideration. In the present paper, claims 1, 8-10, 12, 20, 28-30, 33-35, and 40-43 are amended. Thus, following entry of the present amendment, claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 remain pending and under consideration.

Applicants acknowledge the PTO's withdrawal of the finality of the previous Office Action and kindly thank the PTO for the same. The PTO's sole rejection to the pending claims is addressed below.

I. The Amendments to the Claims

In the present paper, claims 1, 8-10, 12, 20, 28-30, 33-35, and 40-43 are amended. As the amendments to the claims are fully supported by the application as filed, no new matter is presented by the present amendments to the claims.

Claims 1, 8-10, 12, 20, 28-30, 33-35, and 40-43 are amended to delete the word "non-catalytic." Specific support for the amendments to claims 1, 8-10, 12, 20, 28-30, 33-35, and 40-43 may be found, for example, in the specification at page 7, lines 5-21 as filed.

Specific support for the amendments to claim 1, 29, and 30 may be found, for example, in the specification at page 9, lines 10-14 and 20-35, at pages 89-91, Example 15 and Table 1, in the sequence listing, and in claims 1, 29, and 30 as filed.

As the amendments to the claims are fully supported by the application as filed, they present no new matter. Accordingly, entry of the present amendments to the claims is hereby respectfully requested under 37 C.F.R. § 1.111.

II. The Rejection of Claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 as Obvious Should Be Withdrawn

Claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 stand rejected under 35 U.S.C § 103(a) as allegedly obvious over Rouy *et al.* (U.S. Patent No. 6,512,161) and Eggerman *et al.* (IDS 04-06-05) in view of GenBank Accession No. NM_000384, Monia *et al.* (U.S. Patent No. 5,656,612), Agrawal *et al.* (2000, *Mol. Med. Today*, 6(2): 72-81), and Wengel *et al.* (U.S. Patent Application Publication No. 2002/0068708A1), and further in view of Bennet *et al.* (U.S. Patent No. 6,172,216).

In particular, the PTO maintains its assertion that the combination of references teach antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. *See* Office Action, at p. 7. While acknowledging that neither

Rouy *et al.* nor Eggerman *et al.* discloses antisense compounds that are fully complementary to the nucleotide sequence set forth in SEQ ID NO:3, the PTO contends that this deficiency is made up by the GenBank reference disclosing the nucleotide sequence encoding the full-length apolipoprotein B mRNA in combination with Agrawal *et al.*, which allegedly discloses designing antisense oligonucleotide to target the various regions of a known nucleotide sequence of a gene. *See Id.*, at p. 6. The PTO further alleges that Monia *et al.*, Wengel *et al.*, and Bennet *et al.* teach that one or more sugar modifications, phosphorothioate modified internucleoside linkages, 5'-methylcytosine modified nucleobases, and LNA modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. *See Id.*, at p. 7.

Applicants respectfully disagree that the cited references, either alone or in combination, render the invention as presently claimed *prima facie* obvious. Applicants respectfully submit that the cited references, either alone or in combination, do not teach or suggest the presently claimed invention. In particular, Applicants present evidence that the presently claimed antisense oligonucleotide compounds and compositions exhibit greater than 80%, and up to 100%, inhibition of human apolipoprotein B expression. In view of the prior art, which teaches that human apolipoprotein B expression may be inhibited only as much as 80%, Applicants' results demonstrate the non-obviousness of the claims. Nonetheless, even assuming *arguendo* that the PTO has established *prima facie* obviousness of the claimed methods, Agrawal *et al.*, as discussed below, specifically teaches away from excluding the start codon region, further demonstrating the non-obviousness of the claims.

A. The Legal Standard

The Supreme Court's decision in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) sets forth the controlling standard for assessing purported obviousness of a claimed invention: "[T]he scope and content of the prior art are ... determined; differences between the prior art and the claims at issue are ... ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." *See Id.* at 17–18.

The Supreme Court's recent decision in *KSR. Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) provides guidance regarding exactly how the differences between the prior art and claimed invention are analyzed to assess the obviousness or non-obviousness of the claims. As the Supreme Court explained, "interrelated teachings of multiple patents; the effects of

demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art” can all be assessed “to determine whether there was an apparent reason to combine the known elements” as recited by the claim at issue. *See Id.* at 1731. The Supreme Court expressly cautioned that this reason should be explicitly stated. *See Id.* Thus, the PTO must identify an explicit reason to combine the elements of the prior art in the manner defined by the claims at issue. *See Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007)

Moreover, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981 (CCPA 1974). “All words in a claim must be considered in judging the patentability of that claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970).

Where a *prima facie* case of obviousness has been met, it “can be rebutted if the applicant . . . can show ‘that the art in any material respect taught away’ from the claimed invention.” *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997), quoting *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974). “A reference may be said to teach away when a person of ordinary skill, upon reading the reference . . . would be led in a direction divergent from the path that was taken by the applicant.” *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). It is improper to combine references where the references teach away from their combination. *See In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983).

B. The Cited References Do Not Teach or Suggest All Claim Limitations of the Claimed Invention

The presently claimed compounds and compositions recite, *inter alia*, an oligonucleotide compound 20 nucleobases in length, or a salt thereof, targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound (1) is fully complementary to the nucleotide sequence within the range of nucleotides 157 to 13820 of SEQ ID NO: 3; (2) comprises a plurality of nucleosides having modified sugar moieties and a plurality of nucleosides having phosphorothioate internucleoside linkages; (3) demonstrates greater than 80% reduction of apolipoprotein B mRNA levels when applied in vitro at a concentration of 150nM to HepG2 cells; and (4) is not a ribozyme. In an alternate embodiment, the presently claimed compounds and compositions recite, *inter alia*, the oligonucleotide compound that targets a sequence within the range of nucleotides 182 to 13820 or 716 to 9950 of SEQ ID NO: 3.

The combination of cited references, either alone or in combination, fails to render obvious the invention as presently claimed because the combination fails to teach or suggest an oligonucleotide compound that demonstrates greater than 80% reduction of apolipoprotein B mRNA levels. Rather, the primary references cited by the PTO, Rouy *et al.* and Eggerman *et al.*, merely disclose a method for inhibiting apolipoprotein B expression with antisense technology and that antisense oligonucleotides targeted to the apolipoprotein B mRNA may inhibit the mRNA expression by as much as 80%. Further, none of the secondary references cited by the PTO disclose anything regarding inhibition level of antisense oligonucleotides targeted to apolipoprotein B. In contrast, Applicants demonstrate in Example 15 and Table 1, on pages 89-91, that the presently claimed antisense oligonucleotides achieve greater than 80%, and up to 100%, inhibition of human apolipoprotein B expression. For example, ISIS 147788 (SEQ ID NO:25), ISIS 147806 (SEQ ID NO:43), ISIS 147816 (SEQ ID NO:53), and ISIS 147820 (SEQ ID NO:57) show greater than 80%, and up to 100%, inhibition of human apolipoprotein B expression. In addition, Applicants provide working examples, which one of ordinary skill can follow to identify additional antisense oligonucleotides targeted to the nucleotides 157 to 13820 of SEQ ID NO: 3 that exhibit inhibition greater than 80%. Thus, the cited combination of references cited fails to teach every element of the presently claimed invention.

Moreover, the combination of cited references, either alone or in combination, fails to render obvious the invention as presently claimed because the combination fails to teach or suggest an oligonucleotide compound that is fully complementary to the nucleotide sequence within the range of nucleotides 157 to 13820 of SEQ ID NO: 3. As extensively discussed below, Agrawal *et al.* teaches that the start codon region, not the coding region, is the most likely target for antisense inhibition. As such, achieving greater than 80% inhibition by targeting the coding region of human apolipoprotein B mRNA, and excluding the best region suggested to be the best target for designing effective antisense oligonucleotides, further rebuts any conclusion of obviousness.

Although the PTO alleges that the combination of the GenBank reference and Agrawal *et al.* cures this deficiency by teaching antisense oligonucleotide targeting to the various regions of apolipoprotein B mRNA, Agrawal *et al.* cannot be used to reject the presently pending claims as obvious. In particular, the Examiner argues that Applicants' introduction of claim limitation, excluding the start codon region, was only necessitated by the desire to design around the prior art, Agrawal *et al.* See Office Action, at p. 3. Contrary to the Examiner's inference that such a claim amendment bars patentability, applicants are

not prohibited from changing what they regard as their invention during the pendency of the application. *See In re Saunders*, 444 F.2d 599 (CCPA 1971); *see also* MPEP § 2172 (shift in claims permitted). The Examiner further argues that Applicants' assertion that the disclosure of Agrawal *et al.* teaches away from the claimed invention equates to an assertion that Applicants' own specification teaches away from the claimed invention and contradicts Applicants' own disclosure in the specification. *See* Office Action, at pp. 3-4. According to the MPEP, however, "the content of applicant's specification is not used as evidence that the scope of the claims is inconsistent with the subject matter which applicants regard as their invention." MPEP § 2172. Thus, the Examiner cannot dismiss the clear teaching away by Agrawal *et al.*, which is discussed in detail below, by referencing Applicants' own specification.

Therefore, none of the secondary references cited by the PTO, either alone or in combination, cure the deficiency of the combination of Rouy *et al.* and Eggerman *et al.* because they fail to provide a reason why one of ordinary skill in the art should select an antisense oligonucleotide compound that is fully complementary to the nucleotide sequence within the range of nucleotides 157 to 13820 of apolipoprotein B mRNA, which demonstrates greater than 80% reduction of apolipoprotein B mRNA levels. Absent such a reason, the PTO cannot establish obviousness of the present claims under the controlling standard articulated by the Supreme Court. *See KSR* at 1740-41.

Accordingly, for at least the reasons set forth above, the presently pending claims are not obvious over the combination of references cited by the PTO. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C § 103(a).

C. Agrawal *et al.* Teaches Away from the Presently Claimed Invention

Even assuming *arguendo* that the PTO has established *prima facie* obviousness of the claimed methods, any conclusion of obviousness is rebutted because Agrawal *et al.* specifically teaches away from the claimed invention. In particular, Agrawal *et al.* teaches away from an oligonucleotide compound that is fully complementary to nucleotides 157 to 13820 of SEQ ID NO:3, which excludes the start codon region.

At the paragraph bridging pages 76 and 77 of Agrawal *et al.*, the authors discuss the initial step in choosing an appropriate target sequence on the mRNA molecule. The authors state that "it is considered preferable to screen a number of oligonucleotides that encompass different regions on RNA" including the initiation codon site. Agrawal *et al.* at p. 77, col. 1, paragraph 1. Importantly, though, the authors teach that "[o]ligonucleotides that have been

targeted to the translation initiation codon region of mRNA are generally believed to be more potent than those targeted to other regions.” *Id.* Thus, upon reading Agrawal *et al.* as a whole, in combination with the other cited references, a person of ordinary skill would be motivated to target antisense oligonucleotides to the start codon region of apolipoprotein B. Applicants, in contrast, specifically exclude the start codon region in the presently pending claims. Because Agrawal *et al.* leads a person of ordinary skill in a direction divergent from the path that is taken by Applicants, the reference teaches away from the claimed invention, which provides affirmative evidence of non-obviousness. *See Tec Air, Inc.*, 192 F.3d at 1360. As such, Agrawal *et al.* cannot be used as part of an obviousness rejection.

Moreover, as discussed in detail above, the Examiner cannot dismiss the clear teaching away by Agrawal *et al.* by referencing Applicants’ own specification. Further, contrary to the Examiner’s inference that a claim amendment that designs around the prior art bars patentability, applicants are not prohibited from changing what they regard as their invention during the pendency of the application. As such, Applicants respectfully submit that the Examiner cannot maintain the obviousness rejection of the presently pending claims based on these reasons.

Accordingly, for at least this additional reason, the presently pending claims are not obvious over the combination of references cited by the PTO.

D. The Obviousness Rejection Should Be Withdrawn

Applicants respectfully submit that the PTO has failed to establish a *prima facie* case of obviousness for the instantly claimed methods. The references cited by the PTO, whether considered alone or in combination, fail to teach or suggest the invention recited by the presently claimed independent claim 1 of the present application. Moreover, Applicants submit evidence sufficient to rebut any conclusion of obviousness. Thus, Applicants respectfully submit that neither claim 1 nor any of its dependent claims are not obvious over the combination of references cited by the PTO. Nonetheless, even assuming *arguendo* that such *prima facie* obviousness is shown, the prior art references teach away from the presently claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 under 35 U.S.C. § 103(a) as obvious over Rouy *et al.* and Eggerman *et al.* in view of GenBank Accession No. NM_000384, Monia *et al.*, Agrawal *et al.*, and Wengel *et al.* and further in view of Bennet *et al.* withdrawn.

CONCLUSION

In light of the above remarks, Applicants respectfully request that the PTO reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (650) 739-3949, if a telephone call could help resolve any issues.

Respectfully submitted,

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